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ROLE OF CHEMOKINES IN TUMOR GROWTH

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Abstract

Chemokines play a paramount role in the tumor progression. Chronic inflammation promotes tumor formation. Both tumor cells and stromal cells elaborate chemokines and cytokines. These act either by autocrine or paracrine mechanisms to sustain tumor cell growth, induce angiogenesis and facilitate evasion of immune surveillance through immunoediting. The chemokine receptor CXCR2 and its ligands promote tumor angiogenesis and leukocyte infiltration into the tumor microenvironment. In harsh acidic and hypoxic microenvironmental conditions tumor cells up-regulate their expression of CXCR4, which equips them to migrate up a gradient of CXCL12 elaborated by carcinoma associated fibroblasts (CAFs) to a normoxic microenvironment. The CXCL12-CXCR4 axis facilitates metastasis to distant organs and the CCL21-CCR7 chemokine ligand-receptor pair favors metastasis to lymph nodes. These two chemokine ligand-receptor systems are common key mediators of tumor cell metastasis for several malignancies and as such provide key targets for chemotherapy. In this paper, the role of specific chemokines/chemokine receptor interactions in tumor progression, growth and metastasis and the role of chemokine/chemokine receptor interactions in the stromal compartment as related to angiogenesis, metastasis, and immune response to the tumor are reviewed.

Keywords

Chronic Inflammation; Chemokines; Tumor growth; Angiogenesis; Stromal Cells

I. Introduction

Chronic inflammation resulting from low grade, persistent chemical, bacterial, viral agents predisposes the formation of the preneoplastic foci and subsequently promotes tumor development [1-3]. Examples include the links between colon cancer and ulcerative colitis, colorectal cancer and inflammatory bowel disease, pancreatic cancer and chronic pancreatitis, adenocarcinoma of the esophagus and metaplastic premalignant lesions of Barrett's esophagus [1-3]. Of the reported cancer types, majority are attributed to chronic inflammation while some are associated with infectious agents [4]. Examples include viruses {cervical cancer and human papilloma viruses (HPV); hepatocellular carcinoma and hepatitis C viral infection}, bacteria (gastric cancer and *Helicobacter pylori* infection) and parasites (bladder cancer from *Schistosoma* infection). Non-infectious factors such as oxidative stress generating reactive oxygen and nitrogen species (ROS and RNS), produce genetic mutations through the free

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radical attack on DNA and natural aging is associated with the development of spontaneous tumors. Environmental predisposing insults such as ultraviolet light and asbestosis result in chronic inflammation leading to development of melanoma, squamous cell carcinoma and mesothelioma, *respectively* [1-3,5]. The chemical meat processing agents such as nitrates are metabolized into nitrosamines in the gastric mucosa and chronic exposure to nitrosamines leads to development of premalignant foci and eventually gastric carcinoma. Each of these inflammatory insults leads to up regulation of non-specific proinflammatory cytokines such as IL-1 α/β , IL-6, interferon (IFN)- α , and tumor necrosis factor (TNF)- α [6-8]. These cytokines subsequently induce the expression of proinflammatory chemokines [9-12]. Such unresolved chronic inflammation is associated with increased conversion of normal cells to preneoplastic foci.

Accumulation of somatic mutations with gain of function can change preneoplastic foci into neoplastic foci (tumor initiation or cellular transformation) [13]. Activated nuclear factor-*kappa* B (NF- κ B), a transcription factor, links inflammation and tumorigenesis and may be a major factor that controls the ability of both preneoplastic and malignant cells to survive and avoid or escape apoptosis. NF- κ B may also be involved in regulation of tumor angiogenesis and invasiveness [14]. The inflammatory infiltrate containing natural killer cells, macrophages and T lymphocytes may succeed in clearing the initial cluster of tumor cells. Tumor cells with “gain of function” mutations [15], equipped with constitutive activation of anti-apoptotic and proliferative pathways, begin to evolve and modify their microenvironment. Interestingly, the threshold number of mutations that are needed to transform normal human cells is greater than that required for murine cells [16]. There is also immunosuppression through the release of IL-10 and TGF- β from type II tumor-associated macrophages, tumor cells, and fibroblasts [17-20]. These co-coordinated set of molecular events shape the milieu of the tumor foci favoring its growth.

Tumor cells secrete small soluble, molecular chemoattractants, chemotactic cytokines or chemokines that recruit proinflammatory cells and endothelial cells [21]. The resident fibroblasts undergo changes in the newly modified microenvironment and de-differentiate into myofibroblasts or carcinoma-associated fibroblasts (CAFs) expressing a specific marker, α -smooth muscle actin, that is absent in normal fibroblasts [22-25]. These stromal cells (CAFs, proinflammatory leukocytes and cells of vasculature) form the tumor microenvironment. The mutual interaction between the tumor cells and stromal cells orchestrates tumor progression and is mediated by matrix metalloproteinases (MMPs), cytokines, growth factors and chemokines. The autocrine stimulation of tumor cells and reciprocal paracrine stimulation between the tumor cells and the stromal cells facilitate the proliferation of tumor cells. Six traits were reported to be essential for malignant growth: growth autonomy through autocrine stimulatory loops, evasion of apoptosis by constitutive activation of anti-apoptotic pathways, limitless replicative potential, sustained angiogenesis, insensitivity to negative growth signals and acquisition of invasive potential [26]. The presence of chemokines in the tumor microenvironment enables the tumor cells to acquire many of these traits. Chemokines, cytokines like TNF α and growth factors like VEGF and TGF- β are intricately associated with cellular transformation, tumor growth, augmentation of the invasive potential and invasion and metastasis to the distant predilection sites for a particular type of tumor [27-29].

In addition to a role in chronic inflammation associated with tumor progression, chemokines are involved in tumor angiogenesis and in homing of tumor cells to the sentinel lymph nodes, metastasis to specific organs, as well as metastasis of the metastatic lesions. Developmental chemokine cues necessary for cell migration and angiogenesis are duplicated in the tumorigenic process. In the peri- and postnatal life, chemokines are also involved in the homing of leukocytes into the secondary lymphoid organs and the egress and ingress of the leukocytes

from the bone marrow to maintain leukocyte homeostasis and also as an adaptation to the microbial challenges posed to the organism.

This review mainly focuses on the role of chemokine / chemokine receptor interactions in tumor microenvironment that facilitate the tumor growth at the primary site and its metastasis.

A. Chemokines

The chemokines are soluble, small molecular weight (8–14 kDa) proteins that bind to their cognate G-protein coupled receptors (GPCRs) to elicit a cellular response, usually directional migration or chemotaxis [30]. Tumor cells secrete and respond to chemokines, which facilitate growth that is achieved by increased endothelial cell recruitment, subversion of immunological surveillance and maneuvering of the tumoral leukocyte profile to skew it (immunoediting) such that the chemokine release enables the tumor growth and metastasis to distant sites. Thus chemokines are vital for tumor progression.

Chemokines are important in many biological events such as embryogenesis, wound healing, angiogenesis, Th1/Th2 development, leukocyte homeostasis and lymphoid organ development, inflammatory diseases, pro and anti-tumor responses. Based on the positioning of the conserved two N-terminal cysteine residues of the chemokines, they are classified into four groups namely CXC, CC, CX3C and C chemokines [31–34]. The CXC chemokines can be further classified into ELR+ and ELR– chemokines based on the presence or absence of the motif ‘glu-leu-arg (ELR motif)’ preceding the CXC sequence. The CXC chemokines bind to and activate their cognate chemokine receptors on neutrophils, lymphocytes, endothelial and epithelial cells. The CC chemokines act on several subsets of dendritic cells, lymphocytes, macrophages, eosinophils, natural killer cells but do not stimulate neutrophils as they lack CC chemokine receptors except murine neutrophils. There are approximately 50 chemokines and only 20 chemokine receptors, thus there is considerable redundancy in this system of ligand / receptor interaction.

Tumor cells also release soluble mediators such as VEGF-A (Vascular endothelial growth factor-A), TGF β and TNF- α that act on myeloid and endothelial cells and induce the expression of non-classical chemokines such as the S100 chemokine. Interestingly, S100 chemokines are implicated in targeting of the tumor cells to the premetastatic sites or niches rather than the metastatic sites. Probably, S100 chemokines might also be involved in metastasis of metastatic lesions. Specifically, the induced chemoattractants such as S100A8 and S100A9 activate the p38 mitogen-activated protein kinase (p38 MAPK) pathway, resulting in enhanced pseudopodia formation that ultimately increased invasive power of the tumor cells [35,36]. .

VEGF correlated chemokine-1 (VCC-1) is a novel chemokine expressed in breast and colon cancer [37]. Increased VEGF found at tumor sites positively correlated with VCC-1 levels especially in endothelial cells forming tubes *in vitro*. NIH3T3 cells overexpressing the chemokine VCC-1, accelerated tumor development and progression as compared to cells with the control vector injected into mice. Thus VCC-1 probably mediates its effect through increased angiogenesis [37].

Herpes and pox viruses encode chemokine agonists and antagonists that will facilitate the spread of these viruses to their predilection sites [38]. For example, Kaposi's sarcoma-associated herpes virus (HHV8) produces a viral chemokine analog, vMIP-II/K4 that has high affinity for CCR3, CCR8 and CXCR2-expressing cells. The same molecule, vMIP-II/K4 acts as an antagonist for a variety of receptors such as CCR1, CCR2, CCR5, CXCR4, XCR1 and CCR10 [39]. Thus, tumor viruses exploit the host's powerful chemokine system to their advantage.

In Table I, we summarize the chemokines and their corresponding receptors many of which are known to be involved in tumor growth and metastasis through different mechanisms.

B. Chemokine receptors

The chemokines elaborated from the tumor and the stromal cells bind to the chemokine receptors present on the tumor and the stromal cells. The autocrine loop of the tumor cells and the paracrine stimulatory loop between the tumor and the stromal cells facilitate the progression of the tumor. There is redundancy among chemokines as they share chemokine receptors and some chemokine receptors bind more than one chemokine ensures that appropriate biological responses to stress occur. Also, the differences in the affinity of the chemokine interaction with a receptor may impart subtle variations in their biological effects in response to a chemokine ligand [32,40]. This may fine tune and ensure that the ultimate biological responses are achieved. Depending on the cellular type and context, chemokine receptor activation triggers a variety of effector pathways that may include calcium mobilization from intracellular stores and calcium influx through calcium channels, activation of protein kinase C (PKC), phosphoinositide-3-kinase (PI3K), phospholipase C (PLC)- β and *src* family tyrosine kinases (SFK) [30], leading to activation of Rac and Rho whose reciprocal activation and inactivation at the leading and trailing edges of the cell result in directional migration or chemotaxis. Notably, CXCR2, CXCR4, CCR2 and CCR7 play major roles in tumorigenesis and metastasis [41]. CXCR2 plays a vital role in angiogenesis and CCR2 plays a role in the recruitment of macrophages into the tumor microenvironment. CCR7 is involved in metastasis of the tumor cells into the sentinel lymph nodes as the lymph nodes have the ligand for CCR7, CCL21. CXCR4 is of paramount importance as it is mainly involved in the metastatic spread of a wide variety of tumors.

C. Primary tumor growth

Tumor cells and stromal cells undergo co-evolution and with favorable microenvironmental conditions, progress into a well-defined tumor mass. The tumor is comprised of tumor cells and its stromal microenvironment (Fig. 1). The microenvironment is made of extracellular matrix (ECM) and stromal cells. Fibroblasts, cells of vasculature (endothelial cells, pericytes and smooth muscle cells), and inflammatory leukocytes (lymphocytes, macrophages, dendritic cells, mast cells and neutrophils) are collectively called stromal cells. Tumor cells co-opt the stromal cells and may successfully generate increased vasculature, subvert immunity, and induce increased production of MMPs that will facilitate the tumor growth. Each of the components of the tumor contributes to the tumor growth either alone or in combination with other components.

II) Chemokines and tumor cells

The secretion of the chemokines and the cell surface expression of the chemokine receptors on tumor cells facilitate tumor growth and / or metastasis. The two chemokine receptor-chemokine pairs that are involved commonly in many tumors are CXCR4-CXCL12 and CCR7-CCL21.

1) CXCR4-CXCL12 axis

The CXCL12-CXCR4 axis plays a critical role in migration of tumor cells into metastatic sites in breast cancer, ovarian carcinoma, prostate cancer, pancreatic cancer, melanoma, esophageal carcinoma, non-small cell lung cancer, head and neck cancer, bladder carcinoma, colorectal cancer, basal cell carcinoma, osteosarcoma, neuroblastoma, glioma, glioblastoma, acute lymphoblastic leukemia and chronic myelogenous leukemia [41-48]. The chemokine CXCL12 / SDF-1 (Stromal cell derived factor-1) is expressed constitutively in a number of tissues including liver, lung, lymph nodes, adrenal glands and bone marrow, which may explain

why many tumors employ the CXCL12-CXCR4 axis for metastasis (Luker, 2006, 16046252). Physiologically, this CXCR4-CXCL12 axis has been shown to be involved in migration of a subset of embryonic cells involved in the development of the central nervous system, bone marrow and heart [49,50]. The migrational cues employed during embryogenesis seem to be duplicated in tumor progression and metastasis. Recently, it has been reported that SDF-1 can also bind to another chemokine receptor, CXCR7 [51] which is expressed in a number of cells including endothelial cells, T-cells, dendritic cells, B-cells, chondrocytes, endometrial stromal cells. Heesen et al were the first to clone this gene and it was originally named as RDC1 [52]. While SDF-1 interaction with CXCR4 results in chemotaxis [53,54], in the case of CXCR7 it mediates proliferation [55]. SDF-1 secreted by stromal fibroblasts from the tumor microenvironment can binds CXCR4 on tumor cells and stimulates cell motility or chemotaxis as cells respond to an SDF-1 gradient. At the same time, CXCR7 expressed on tumor cells can produce a proliferative effect [55]. Thus SDF-1 can modulate the migrational capacity of tumor cells and CXCR7 can enhance tumor growth.

Hypoxia and CXCR4—Under normoxic conditions in the tumor area, von Hippel-Lindau (VHL) tumor suppressor protein pVHL negatively regulates CXCR4 expression by stimulating the degradation of hypoxia inducible factor (HIF-1- α). Hypoxic or ischemic conditions present in the tumor cell mass promote the transcription and translation of HIF-1- α . Interestingly, a mutant BRAF (V600E) signaling molecule induces HIF-1- α expression in melanoma [56]. HIF-1- α then induces the expression of CXCR4 [57,58]. This is true not only for the tumor cells but also for human microvascular endothelial cells (HMEC) [59]. It is noteworthy that the chemokine CXCL12 is expressed constitutively in different tissues such as liver, lung, lymph nodes, adrenal glands and bone marrow. These CXCL12-rich organs may serve as fertile ground for the tumor cells with up regulated CXCR4 expression on their plasma membrane. Hypoxia also reversibly inhibits macrophage migration [60]. Stationary macrophages in hypoxic environment may elaborate chemokines that promote survival of tumor cells. Thus, CXCL12 plays a crucial role in survival and metastasis of the tumor cells.

Recently, a linkage has been made between metastasis and angiogenesis through CXCL12/CXCR4 signaling. A glycolytic enzyme, phosphoglycerate kinase (PGK) has been found to be angiostatic, as the secreted PGK from tumor cells cleaves extracellular plasminogen to produce angiostatin. In metastatic sites, a high level of CXCL12/CXCR4 signaling down regulates PGK1 expression that releases the angiostatic clamp. This angiogenic switch has been proposed to be very important for the survival of the metastasized colony of tumor cells and also for metastasis from the metastatic site [61].

2) CCR7-CCL21

The chemokine ligand-receptor pair; CCL21-CCR7, plays a key role in the migration of tumor cells into the sentinel lymph nodes in many tumors including breast cancer [62], murine B16 melanoma [63], non-small cell lung cancer (NSCLC) [43], colorectal cancer [64], gastric carcinoma [65], esophageal cell carcinoma [44] and head and neck cancer [41]. The abundance of CCL21 in the lymph nodes chemoattracts tumor cells bearing the chemokine receptor CCR7. Interestingly, murine CCL21 (but not human CCL21) also transduces through CXCR3 and so murine tumor cells bearing CXCR3 can metastasize to lymph nodes in addition to CCR7. Thus, therapeutic disruption of the CCR7/CCL21 may prevent lymph node metastases but this depends on early detection of the primary tumor.

3) Breast Cancer

Chemokines and breast cancer—The chemokine CCL2 / MCP-1 (Macrophage chemotactic protein-1) is highly expressed in breast tumor [66] and stromal cells. Tumor-associated macrophages (TAM) in the tumor stroma exhibit elevated expression of CCL2 and

high TAM accumulation correlates with disease recurrence and poor prognosis [67,68]. Further, neutralizing antibodies to CCL2 prevented the formation of the lung metastases in mice bearing CCL2-expressing MDA-231 human breast carcinoma xenograft [69]. This suggests that CCL2 contributes to the metastasis of breast carcinoma cells. In estrogen receptor (ER)-negative breast tumor cells, the cancer-associated membrane glycoprotein, dysadherin, promotes invasion of tumor cells into the matrigel through regulation of CCL2 expression *in vitro* and lung metastasis in an *in vivo* animal model [70]. Thus increased CCL2 expression as a result of overexpression of dysadherin may facilitate breast tumor progression and metastasis.

The level of CXCL8 is inversely correlated with estrogen receptor expression in breast cancer, but no correlation is observed for its receptor CXCR2 [71]. Estrogen-receptor negative breast tumor cells elaborated more CXCL8 than the ER-positive tumor cells. Interestingly, increased CXCL8 expression positively correlated with HER2 expression [66]. The increased CXCL8 expression level reflected in increased invasiveness of breast cancer cells into matrigel [72]. Conditioned media from such tumor cells also promoted angiogenesis *in vivo* when injected subcutaneously into nude mice [72]. The exacerbated level of CXCL8 in invasive breast cancer cells was attributable to the transcription factors NF- κ B, AP-1 and C/EBP acting on the CXCL8 promoter [73]. Interestingly, depletion of the tumor suppressor 'Tumorous Imaginal Disc1' (Tid1) enhanced the mRNA level of CXCL8 *in vitro* [74].

Elevated levels of the chemokine CCL5 / RANTES (regulated upon activation, normal T cell expressed and secreted) have been frequently observed in advanced stage breast carcinoma [75] and this potentiates the invasiveness of the breast cancer cells. The reciprocal interactions between breast tumor cells and TAMs through soluble mediators such as inflammatory cytokines, MMPs and angiogenic factors form a vicious cycle. For example, TNF- α released from TAMs can stimulate the expression of the chemokines CCL2 and CCL5 in breast cancer cells which attracts even more TAMs, thus completing the vicious cycle [76].

Chemokine receptors and breast cancer—Breast cancer cells express CXCR4 and CCR7 which bind CXCL12 and CCL21 / 6Ckine, respectively [62]. Many breast tumor cell lines including MDA-MB-231, MDA-MB-436, MDA-MB-468, SK-BR-3, BT-474, CAMA-1, T47D, ZR-75 express CXCR2 but feebly expressed in MCF-7 based on RT-PCR (Reverse-Transcriptase-Polymerase Chain Reaction) [71]. Armed with CCR7 expression, the breast cancer cells can metastasize to the sentinel lymph nodes that express CCL21 [62]. Also, chemokine activated CXCR4 and CCR7 facilitate F-actin and pseudopodia formation in tumor cells and induce chemotactic and invasive responses in breast tumor cells [62]. So, CCR7 may navigate the homing of the breast tumor cells to the draining sentinel lymph node and CXCR4 may facilitate in the metastasis from the lymph nodes to the distant sites that constitutively express CXCL12.

Interestingly, a positive correlation between HER2 receptor activation and increased expression of CXCR4 is seen in some breast cancer patients. Also, there is an inhibition of ligand-induced degradation of CXCR4. Based on these two experimental observations, Zlotnik speculated that part of anti-HER2 antibody (Herceptin) mediated therapeutic effect may be due to the down-regulation of CXCR4 activity in breast tumor cells [41].

CXCR3 is expressed in many breast cancer cell lines including MDA-MB-231, MCF-7 and T47D [77]. These cell lines also elaborate CXCL10, the chemokine ligand for CXCR3, indicating the operation of an autocrine loop. Serum starvation and exposure to increasing concentrations of CXCL10 increased the cell surface CXCR3 expression in these cell lines. In a murine model of breast cancer, small molecule inhibitor of CXCR3 antagonized the lung metastasis of the highly malignant mammary tumor cell line 66.1 [78]. This indicates that CXCR3 can mediate lung metastasis of breast cancer cells.

4) Melanoma

Chemokines and melanoma—Melanoma cells elaborate a battery of chemokines such as CXCL1–3 / MGSA (Melanoma growth stimulatory activity)- α , β and γ / GRO (Growth-regulated oncogene)- α , β and γ [79-82], CXCL8 [83], CCL5 [82] and CCL2 [84]. They also express chemokine receptors especially CXCR4, CXCR2, CXCR3, CCR7 and CCR10 [59, 62,85-88].

Over expression of CXCL1, 2, or 3 in immortalized melanocytes induced their ability to form tumors [80,89]. CXCL1 isolated from Hs294T melanoma cell culture supernatants showed autocrine growth stimulatory activity [79,80] and was described as a growth-related oncogene [82,90]. CXCL1 mRNA is constitutively expressed in cultured nevocytes from benign and dysplastic nevi and melanoma cells but undetectable in isolated primary melanocytes [91]. Melanoma cells acquire the ability to express CXCL1 constitutively through NF- κ B activation [92].

CXCL8 is constitutively expressed by many melanoma cell lines *in vitro*. CXCL8 / IL-8 is mitogenic for melanoma cells as indicated by the decrease of melanoma cell proliferation by neutralizing monoclonal antibodies against CXCL8 and by decreasing CXCL8 expression by transfection of melanoma cells with anti-sense oligonucleotides [93]. Interestingly, in nude mice, the human melanoma cells that metastasized to different organs expressed different levels of CXCL8. Metastatic human melanoma cells harvested from subcutaneous area express higher levels of CXCL8 as compared to those from the liver. These melanoma cells with higher CXCL8 expressing capability when reinjected and reharvested from metastatic liver lesions produced lower levels of CXCL8. These results were reproduced from co-culture experiments involving melanoma cells with keratinocytes and melanoma cells with highly differentiated hepatocytes *in vitro*. The reason for this change in CXCL8 expression is through paracrine induction of CXCL8 in melanoma cells by IL-1 derived from the keratinocytes of the skin and the negative regulation of CXCL8 expression by TGF- β from the hepatocytes. This highlights the role played by tumor microenvironment in melanoma progression and metastasis [94].

The chemokine CCL5 is secreted by a subset of melanoma cells. The CCL5 level is up regulated by TNF- α in the melanoma microenvironment and the ability to form aggressive melanoma positively correlates with the level of CCL5 in nude mice [95]. CCL5 is also a chemoattractant for the leukocytes and may aid in recruitment of the necessary leukocytes that favor melanoma progression.

CCL2 has also been shown to be associated with certain stages of melanoma progression accompanied by infiltration of macrophages into the tumor [96]. CCL2 induces MMP secretion by macrophages that would facilitate the dissemination of the melanoma cells [86].

Chemokine receptors and melanoma—The mRNA for the chemokine receptors CXCR4, CCR7 and CCR10 are expressed at elevated levels in melanoma compared to primary melanocytes. These bind their respective ligands CXCL12, CCL21 and CCL27 / CTACK that are expressed at a high level in their metastatic locations such as lymph node, lung, liver, bone marrow and skin. CCL27 is a skin-specific chemokine [97] and is up-regulated by the chronic inflammatory environment containing IL-1 and TNF- α [Homey, 2000, 10725697]. The receptor for the chemokine CCL27, CCR10, is expressed by a variety of cells in the skin including, melanoma cells, melanocytes, dermal fibroblasts, Langerhans cells, endothelial and T cells [98]. CXCR1 and CXCR2 are also reported to be expressed in melanoma cells [99, 100], though Muller *et al* did not observe enhanced expression of CXCR2 in melanoma [62].

In a mouse model of melanoma, angiostatic activity of CXCR3 has been found when its ligand CXCL10 was expressed in the tumor [101]. In another mouse model, when B16F10 melanoma

cells (endowed with constitutive CXCR3 expression) were injected subcutaneously into C57BL/6 mice, the mice had robust metastasis to lymph nodes. When the same cell line was used with CXCR3 silenced, the lymph node metastatic frequency was markedly reduced. Also, pretreatment with Freund's complete adjuvant increased the levels of CXCL9 and CXCL10 in the draining lymph nodes and this was followed by increased metastatic frequency to the lymph nodes with larger foci [87].

5) Lung Cancer

The importance of the tumor microenvironment and the role played by CXC chemokines is prominent in lung cancer [102]. CXCL8 expression appears to be modulated through autocrine and paracrine interactions between the tumor cells and infiltrating macrophages. The macrophages that infiltrate the tumor “educate” or induce the lung cancer cells to elaborate CXCL8 that promotes angiogenesis. These macrophage-sensitized lung tumor cells when co-cultured with freshly isolated lung cancer cells exhibit a 35% increase in CXCL8 mRNA [103]. TNF- α and IL-1 α can induce a dose-dependent increase in CXCL8 expression in lung

tumor cells. Blocking TNF- α and IL-1 α with neutralizing antibodies reduced CXCL8 expression even in macrophage-sensitized lung tumor cells.

i) Non-small cell lung cancer (NSCLC)—CXC chemokines are very vital for non-small cell lung cancer [102]. CXCR4 has been implicated in the metastatic process of NSCLC and the receptor CCR7 in lymph node metastases [41,43]. Production of prostaglandins (has a high inflammatory potential) is elevated in NSCLC tumor due to a constitutive elevation of cyclooxygenase-2 (COX-2), the rate limiting enzyme in prostaglandin production. Pold et al found that COX-2 up-regulates the expression of CXCL5 and CXCL8 through production of the eicosanoid, PGE₂, in NSCLC cell lines A549 and H157, where the COX2 gene has been modified [104]. Conceivably, in the SCID mouse model of NSCLC, neutralizing CXCL5 and CXCL8 reduced tumor growth by blocking their angiogenic potential [104].

The elevated expression of CXCL12 as assessed by enzyme linked immunosorbent assay (ELISA) and immunohistochemistry has been observed from stage IA to IIB of human NSCLC tumor samples [105]. This increased elaboration of CXCL12 correlated with increased inflammation and more infiltration of CD4⁺CD69⁺CXCR4⁺ T cells compared to normal lung parenchyma and approximately 30% of these cells expressed the regulatory T cells (T_{reg}) markers CD25^{high} and FoxP3. CD4 T cells displayed increased chemotaxis to CXCL12 and they expressed elevated levels of CXCR4. In sum, CXCL12 expression may influence tumor progression by shaping the leukocyte infiltrate of lung adenocarcinoma [105]. The CXCL12 / CXCR4 axis also facilitates NSCLC cells to migrate into the pleural space and replication of these cells cause intensive damage to the host with pleural effusion with ensuing pleurisy and dyspnoea.

ii) Small cell lung cancer (SCLC)—Small cell lung cancer is an aggressive, rapidly metastasizing tumor. However, SCLC cells produce low levels of common pro-angiogenic chemokines. Zhut et al have shown that SCLC cell lines H711, H69, H345, Lu165 and GLC19 produce CXCL6 / GCP-2 constitutively and this was mediated by NF- κ B. ALLN, a NF- κ B inhibitor that prevents I κ B degradation, abolished CXCL6 production almost completely [106]. In addition, IL-1 β and hypoxia significantly up-regulated the production of CXCL6 in SCLC cell lines. Thus, CXCL6 promotes tumor progression under hypoxic conditions. Proliferation of SCLC cell lines through the operation of CXCL6 autocrine loop is evident from inhibition of proliferation by neutralizing anti-CXCL6 antibodies [106].

SCLC cells express high levels of CXCR4. Activation of CXCR4 by CXCL12 in SCLC cells induced integrin activation (α 2, α 4, α 5 and β 1 integrins) and resulted in increased adhesion to

extracellular matrices, fibronectin and collagen [107] making them more chemoresistant. This integrin activation could be inhibited by the CXCR4 antagonist, T140. Stromal cells also protect SCLC cells from apoptosis induced by chemotherapy and this could also be antagonized by CXCR4 inhibitors [107]. This highlights the importance of CXCL12/CXCR4 axis mediated tumor cell adhesion and survival during chemotherapy and harsh microenvironmental conditions [107]. On the other hand, CXCL4 has angiostatic property through its binding to CXCR3 in lung cancer [108]. In an advanced lung cancer murine model of spontaneous bronchoalveolar carcinoma, intranodal injection (axillary lymph node) of another chemokine, CCL19, reduced the SCLC tumor burden markedly [109]. This might be due to increased recruitment of dendritic cells and T cells by the exogenous CCL19.

6) Prostatic carcinoma

The mRNA for the chemokine CCL5 has been shown to be expressed in the human prostate cancer cell lines including PC-3, DU-145 and LNCaP and also in primary prostate adenocarcinoma cells [110]. CCL5 induces proliferation and stimulation of invasive power of prostate cancer cells and this effect is inhibited by the CCR5 antagonist TAK-779 [110]. The chemokines CCL2 and its receptor CCR2 has been reported to be present in human prostate cancer cell lines including PC-3, VCaP, C4-2B, LNCaP, hFOB and primary prostate epithelial cells [111,112]. Similar to CCL5, CCL2 is also involved in proliferation and migration of prostate cancer cells by acting in an autocrine and paracrine manner and this effect can be abrogated by directing neutralizing antibodies against CCL2 [113]. Neutralization of the CCL25-CCR9 interaction indicated that the chemokine receptor CCR9 plays a role in prostate cancer cell migration, invasiveness and expression of MMPs [114].

In the human PC3 tumor / SCID mouse model, CXCL8 plays an important role in tumor growth and angiogenesis whereas in Du145 model, CXCL1 is involved. Neutralizing antibodies against CXCL1 and CXCL8 inhibited the tumor growth confirming the involvement of both CXCL1 and CXCL8. CXCL8 has also been implicated in the prostate tumor growth in an androgen-independent manner [115,116]. Interestingly, TGF- β 1 up regulates CXCL8 expression level in human prostate cancer cell lines [117].

'Transgenic adenocarcinoma of the mouse prostate' (TRAMP) mice with the CXCR2^{-/-} background have tumors significantly smaller than the TRAMP/CXCR2^{+/+}. On the other hand, TRAMP/CXCR3^{-/-} mice developed palpable tumor earlier and had increased angiogenesis than TRAMP/CXCR3^{+/+} mice. This implies that CXCR3 represents the counter-regulatory mechanism that inhibits the prostate tumor growth [118,119].

The chemokine receptor CX3CR1 is expressed human prostate cancer cells. The ligand for this receptor, the plasma membrane-bound CX₃CL1 is expressed in human bone marrow endothelial cells that enables the tumor cells to activate the PI3K/Akt survival pathway in the tumors that have metastasized to the bone [120].

CXCR4 is undetectable in prostatic hyperplasia cell lines but in prostatic carcinoma cell line, PC-3, its expression is induced [121]. Tumor associated fibroblasts (TAFs) or CAFs seem to direct tumor progression after tumor initiation in the prostate [122]. Incubation of initiated but non-malignant prostatic epithelial cells (BPH-1 cells) with TGF- β induced cell surface expression of CXCR4 and promoted malignancy when xenografted with TAFs under the kidney capsule of mice. This may be due to cross-talk between paracrine TGF- β and the chemokine CXCL12-induced pathways in BPH-1 cells [123].

The normal prostate epithelial cell line (PZ-HPV-7) produces lower amounts of CXCL1 and CXCL8 and higher amounts of CXCL10 and CXCL11. When CXCL10 was overexpressed in

the LNCaP prostate tumor cell line, it inhibited cell proliferation by 40% and decreased prostate-specific antigen (PSA) production by up regulating CXCR3 receptor [118,119].

The regulation of the prostate tumor growth by the Duffy antigen / receptor for chemokines (DARC) is well documented. DARC, a silent non-signaling chemokine receptor, is expressed on both erythrocytes and endothelial cells. DARC acts as a CXC chemokine sink and the absence of which leads to abundance of chemokines and aberrant tumor cell growth. About 70% of men of African descent lack DARC expression in the erythrocytes. The incidence of prostate cancer in African americans is significantly elevated as compared to that of Caucasians. Recently, a tumor suppressor protein 'KAI1' has been found on prostate tumor cells. KAI1 directly binds DARC on endothelial cells leading to reduced tumor growth through induction of senescence of tumor cells [124,125]. Tumor cells that loose KAI1 expression escape DARC-based control and grow unimpeded. The role played by DARC on endothelial cells is described in detail in the 'endothelial cell section'.

7) Multiple myeloma

Multiple myeloma (MM) is a B cell tumor and it is the second most common adult hematological malignancy. MM is characterized by the clonal expansion of malignant plasma cells in the bone marrow, the presence of monoclonal antibodies in the serum, suppression of normal antibody production and the activation of osteoclasts that leads to osteolysis. Pathologically, multiple myeloma causes extensive skeletal destruction with osteolytic lesions that result in severe bone pain, fracture and hypercalcemia. MM cells in the bone marrow originate from lymph nodes, navigate across the endothelial sinuses of bone marrow and localize in that microenvironment establishing contacts with the stromal cells [126]. The interaction of the MM cells with bone marrow stromal cells is important for homing and proliferation of MM cells in bone marrow microenvironment and for induction of osteoclast proliferation and activation [127]. The chemokines and chemokine receptors play a pivotal role in the pathogenesis of the multiple myeloma. MM express high levels of the chemokine receptors CXCR3, CXCR4, CCR1, CCR5 and CCR6. They also elaborate many chemokines including CCL3, CCL2, CXCL8 and CXCL12 [128,129].

Chemokines and multiple myeloma—The chemokines CCL3 and CCL4 are constitutively expressed by MM cells. These chemokines induce osteolytic bone lesions. Bone marrow stromal cells express the receptors for CCL3, CCR1 and CCR5. CCL3 induces IL-6 production by bone marrow stromal cells. IL-6, a major cytokine in multiple myeloma, induces more bone resorption through increased proliferation and activity of osteoclasts [130]. CCL3 also stimulates the proliferation, migration and survival of plasma cells by the activation of Akt and ERK pathways [131]. CCL3 is responsible for anemia in multiple myeloma patients by acting on CCR1 expressed by erythroid precursors and suppressing their proliferation [132].

CXCL12 is constitutively expressed at high levels by bone marrow stromal cells that act on CXCR4 and promote transendothelial migration of myeloma cells. This is through up-regulation of the integrins VLA (very late antigen)-4 ($\alpha 4\beta 1$) / VCAM (Vascular cell adhesion molecule)-1 on MM cells enabling them to adhere to the endothelium in the bone marrow microenvironment [126]. The CXCL12 / CXCR4 axis facilitates homing of myeloma cells to the bone marrow in 5TMM syngeneic murine model (aged C57BL/KalwRij mice that spontaneously develop multiple myeloma) [133].

CXCL11, CXCL9 and CXCL10 are primarily produced by macrophages and act on CXCR3 present on many myeloma cell lines to induce chemotaxis. These chemokines also enhance total phosphotyrosine level and stimulate secretion MMP-2 and MMP-9, both of which are involved in tumor progression, invasion and metastasis in advance stages of multiple myeloma

[128]. The myeloma cells are reported to express both isoforms of CXCR3 (CXCR3-A and B). Interestingly, the CXCR3 expression was cell cycle dependent [134]. Also, the endothelial cells from the bone marrow of the multiple myeloma patients elaborate elevated levels of CXCL8, CXCL11, CXCL12, and CCL2 as compared to the endothelial cells from control human umbilical vein endothelial cells (HUVEC). These CXC chemokines efficiently stimulate chemotaxis of MM cells. In addition, CXCL8 and 12 stimulate proliferation of these cells [129].

CXCL8 has been shown to be up regulated by endogenous aberrant expression of CD28 on myeloma cells apart from normal secretion by bone marrow stromal and endothelial cells. This surge in CXCL8 increases receptor activator of NF- κ B ligand (RANKL) expression in osteoblasts thus altering the RANKL / osteoprotegerin (OPG) ratio in cells. This altered ratio favors osteoclast formation which might trigger the bone pathology in multiple myeloma. CXCL8 can also induce proliferation and chemotaxis of multiple myeloma cell lines and isolated plasma cells from multiple myeloma patients. Thus, CXCL8 plays an important role in multiple myeloma-induced osteolysis [135-138].

CCL2 produced by bone marrow stromal cells attracts CCR2-bearing MM cells to bone marrow. MM cells produce the cytokines IL-6 and TNF- α which up regulate CCL2 inducing migration of more MM cells into the bone marrow. CCL2 thus plays a role in homing and tumor progression in multiple myeloma [139-141].

8) Colorectal cancer

In colon cancer, genes reported to be up-regulated include chemokines (CCL2 and CXCL1), cyclooxygenase-2 (COX2), growth factors (VEGF and TGF β 2), and cytokines (IL-6) [11, 142-145]. In a mouse model of colitis-associated cancer, IKK β , an upstream activator of NF-

κ B, has been reported to link inflammation with tumorigenesis as the conditional knockout of IKK β in colonic epithelial cells significantly attenuated the tumor incidence and deletion in myeloid cells significantly reduced the tumor size [146]. NF- κ B activation transcriptionally up regulates many chemokines involved in tumor progression and metastasis.

CXCR3 is constitutively expressed in several colon cancer cell lines including Colo205, HCT116, HT29, RKO and WiDr. The cell line DLD-1 which lacks endogenous expression of CXCR3, when endowed with CXCR3 expression exhibits enhanced metastasis to lymph nodes [147]. Furthermore, clinical samples of human colon cancer when positive for CXCR3 exhibit lymph node metastasis which is correlated with poor prognosis [147]. CXCL10 and CXCR3 are significantly increased by IFN- γ treatment of colon cancer cell lines [148]. In addition, CXCL10 induces matrix metalloproteinase 9 (MMP-9) expression and increased cell migration [148].

9) Ovarian Carcinoma (OC)

In ovarian cancer cells, only CXCR4 expression was detected of the 14 chemokine receptors investigated [149]. Invasion by IGROV, an ovarian cell line, was completely inhibited by TNF- α converting enzyme inhibitor Marimastat indicating that TNF- α plays a major role in ovarian tumorigenesis [149]. Interestingly, the CXCR4 expression level correlated with the TNF- α

level in primary ovarian epithelial cancer cells and clinical biopsies. This was primarily due to increased de novo synthesis of CXCR4 mRNA and protein. Activation of CXCR4 by CXCL12 induces transactivation of the epidermal growth factor receptor (EGFR) in ovarian cancer cell lines [150]. Also, there was an increase in the level of argininosuccinate synthetase, an enzyme involved in the production of nitric oxide, proline, pyrimidines and polyamines that are very vital for tumor cell growth [151]. When TNF- α was neutralized with an antibody or

silenced by RNAi, CXCR4 mRNA and protein was down regulated [152]. Also, with constitutive production of TNF- α there was a significant increase in elaboration of CXCL12 and CCL2. Stable silencing of TNF- α resulted in significantly low levels of CXCL12, CCL2,

VEGF, IL-6 and MIF (Macrophage Migration Inhibitory Factor) [153]. Cell surface CCR2 expression in macrophages associated with human ovarian carcinoma was reduced due to an increase in the TNF- α in the ovarian tumor microenvironment [154]. Interestingly, CXCL12 and VEGF synergistically induce neovascularization in the tumor microenvironment [155]. Also, tumor-associated plasmacytoid dendritic cells induced angiogenesis through production of TNF- α and CXCL8 [156].

CXCL1 and CXCL8 secretion by ovarian cancer cell lines including SKOV-3, PE01, OVCAR-3, OV167, and OV207 was detected by mass spectrometry [157]. In ovarian tumorigenesis, it has been proposed that there is reprogramming of the tumor-resident fibroblasts toward senescence through the action of CXCL1 secreted by the tumor cells. This CXCL1-induced fibroblast senescence seems to be a requirement for tumor promotion in ovarian tumor reconstitution studies [158-160].

III) Chemokines and leukocytes

One prevailing view which underscores the importance of chemokines in tumor progression is that chronic inflammation plays a role in cancer progression. Chemokines attract leukocytes and lymphocytes to the site of inflammation. Chemokines have both pro- and anti-tumor effect within the tumor microenvironment by regulating immune cell infiltration. Generally, CXC chemokines attract neutrophils and lymphocytes while CC chemokines attract lymphocytes and monocytes [1]. Leukocytes infiltrate the tumor in response to chemokines secreted by the tumor tissue, or stroma. This immune cell recruitment may promote anti-tumor activities such as elimination of tumor cells by macrophages and recruitment of innate and adaptive immune cells.

However, later in the tumor progression, the attraction of immune cells by chemokines causes more harm than good. Ehrlich, Mantovani, Balkwill, Pollard and others have shown that tumor secreted chemokines and other factors bring in leukocytes in order to increase tumor growth and supply survival factors as well as angiogenic mediators for tumor vasculature. In many cases, the receptors for a particular chemokine are up regulated in tumor cells which allow them to take advantage of the persistent chemokines in their microenvironment. Thus, immune cells' ability to secrete chemokines can be considered hijacked by the tumor for its progression. For example, macrophages present in the neoplastic lesions secrete chemokines that are involved in tumor cell proliferation and survival, matrix remodeling, angiogenesis and metastasis.

Although there are many members of immune system participating in the tumor microenvironment, this section will focus on the ones that may have more prominent roles being regulated by the chemokines.

1) Tumor Associated Macrophages (TAM)

Macrophages are derived from monocytes recruited to the neoplastic sites and stimulated by specific chemokines secreted by tumor cells, namely CCL2 [161]. CCL2 is also secreted by the TAMs [67]. CCL2 is widely expressed in many human carcinomas and its production corresponds to the macrophage recruitment [162,163]. In some studies, TAMs and CCL2 have been implicated to have pro-tumorigenic role. For instance, in breast and esophageal cancers, CCL2 expression is correlated with high TAM influx, lymph node metastasis and a poor prognosis [164].

However, the CCL2 effect on neoplastic cells appears to vary with the amount in the tumor microenvironment. In melanoma, low expression of CCL2 with modest macrophage infiltration promotes tumor growth whereas high expression of CCL2 recruits a large number of macrophages and exerts anti-tumor activities [165]. TAMs possess tumor killing ability after being activated by IL-2, IL-12 and IFN- γ [3]. However, TAMs from ovarian cancer have defective CCR2 and do not respond to CCL2 [154]. In pancreatic cancer patients, a high level of CCL2 is associated with high infiltration of macrophages and a good prognosis [166].

Likewise, another inflammatory chemokine, CCL5 has a similar effect, acting as an anti-tumor agent, in non-small-cell lung cancer and is associated with an active lymphocytic response [167]. However, CCL5 may be involved in tumor progression, as evidenced by the study showing that CCL5 expression correlates with the more advanced tumor stages in breast carcinoma [75,168]. As observed in the examples of CCL2 and CCL5, certain chemokines have two opposing effects on tumor progression. The occurrence of one of these two effects may depend on the context of the tumor, such as the presence of other cellular and molecular mediators, or the amount of chemokines present.

In addition to the above two chemokines, pico- to nanomolar amounts of CCL3, CCL4, MCP-2/CCL8 and CCL22 are detected in the ascites cells and fluid in ovarian cancer, which correlates with macrophage and T cell infiltration [169]. In ovarian cancer, CCL18 highly expressed by TAMs is detected in ascitic fluids [170]. This chemokine has been previously shown to be derived from dendritic cells and to attract naïve T cells [171].

TAMs recruited and stimulated by chemokines can benefit tumor growth, invasion and angiogenesis. TAMs produce growth factors such as epidermal growth factor (EGF) and transforming growth factor (TGF β), benefiting tumor cell proliferation [164]. Kleeff *et al.* (1998) observed that TAMs expressed MIP3- α /CCL20 abundantly and stimulated growth and migration of two of four CCR6 positive pancreatic cancer cell lines tested [172]. Furthermore, CCL2, CCL4 and CCL5 induce macrophages to produce MMP9, which digest the extracellular matrix and promote tumor migration away from the primary site or leukocyte infiltrating the tumor [28,168,173]. CCL2 and CCL5 also increase production of angiogenic factors, CXCL8 and VEGF by monocytic cells [174]. In addition to the production of tumor promoting factors, chemokine-regulated TAMs may counteract anti-tumor activities via immune subversion. Leukocytes persistently exposed to the chemokines in the context of tumor assume a type II macrophage phenotype, which suppresses the immune response by the secretion of IL-10 and TGF- β [17]. This mechanism allows the tumor to escape the immune destruction.

2) Dendritic Cells

Dendritic cells (DC) are one of tumor infiltrates which capture the antigens and stimulate T cells at the lymph nodes after maturation. Chemokines secreted in response to inflammatory conditions lead to an influx of immature DCs. After being activated by the tumor or foreign antigens, DCs change their chemokine receptor expression so that they can travel to secondary lymphoid organs.

Many cancers have been known to secrete chemokines that cause tumor infiltration of DCs. CCL20 produced by neoplastic cells in pancreatic carcinoma, renal cancer, breast carcinoma and papillary thyroid carcinoma and by TAMs in pancreatic cancer attract CCR6 expressing DCs [175]. Likewise, over expression of CCL20 has been shown to attract a massive number of DCs that activate tumor specific cytotoxic T cells [176]. CXCL12 and CCL5 are also known to attract immature DCs to the tumor site via CXCR4 and CCR5 [177,178]. Immature monocyte-derived DCs can chemotactically respond to BRAK/CXCL14 and this chemokine is absent in many human cancer cells, implying the tumor immunologic escape [179].

After being recruited to the tumor, DCs engulf the tumor antigens, present them on MHC molecules and become activated. Activated DCs upregulate CCR7 thus become responsive to MIP-3 β /CCL19 and CCL2. These chemokine ligands and receptors enable dendritic cells to migrate to secondary lymphoid organs, where they stimulate T cells and mount immune reactivity [178]. Hirao *et al.* observed that when injected to the periphery of the tumor, DCs expressing CCR7 had a greater ability to migrate to the draining nodes compared to non-expressing DCs [180]. They also showed that CCR7 was up regulated whereas CCR1 was down regulated in DCs co-cultured with apoptotic tumor cells. Thus, CCR7 seems to be one of the important factors for the anti-tumor activity of DCs. Consistently, secondary lymphoid organ chemokines are known to decrease tumor burden [181], presumably due to more DCs draining to the lymph nodes and triggering immune responses against tumors.

Yet, the role of tumor associated DCs in tumor progression has remained ambiguous. Generally, increased number of DCs associated with tumor would result in more immune responses to the tumor. MCP-3/CCL7 recruited DCs in the tumor periphery are associated with a good prognosis in human carcinoma [175]. Similarly, plasmacytoid DCs can produce a large amount of type I interferons which possess anti-tumor property and stimulate more immune responses [178].

However, it is counterintuitive that tumor cells would secrete chemokines that recruit agents against themselves. As explained by Balkwill *et al.* and others, cancer progression is Darwinian selection for factors and mediators fostering the tumor growth and survival [182]. Thus, not surprisingly, there is evidence suggesting that tumors interrupt DCs' normal function to generate immune responses. Melanoma and colorectal cancer cells have greater tendency to recruit immature DCs than mature ones. DCs treated with conditioned medium from melanoma cell lines exhibited greater adherence to the tumor cells and become unresponsive to CCL21, a chemokine secreted by the lymphatic vessels [183].

3) T cells

T cells are part of the adaptive immunity that the host possesses against tumor as naïve T cells circulate in the blood stream and secondary lymphoid organs, they recognize the antigens on antigen presenting cells (APCs) such as DCs. Upon stimulation with the specific antigen (for example, tumor specific antigen), they become effector and memory T cells and travel to the tissues for inflammatory responses. Chemokines and chemokine receptors are expressed on naïve and activated T cells. For instance, naïve T cells are reported to express CXCR4 and CCR7. Activated T cells are responsive to CCL5, CCL2, CCL8 and CCL7; and express CXCR5 and CXCR3 [184]. Similar to macrophages, T cell infiltration to the tumor may mean both pro- or anti-tumor survival.

A study from Negus *et al.* shows that CCL5 is associated with the recruitment of CD8⁺ T cells infiltration, which presumably have the cytotoxic activity against tumor [185]. Similarly, CCL16 has been shown to attract APCs, T cells and granulocytes and lead to tumor rejection by cytotoxic T cells in a mouse mammary adenocarcinoma model [186]. Mouse6Ckine (CCL21 in human), when transfected into colon carcinoma cell line, exerts anti-tumor function mediated by CD8⁺ T cells in addition to angiostatic mechanisms [187].

On the other hand, chemokines may mediate T cell anergy, disabling their ability to destroy neoplastic cells. In this context, polarizing T cells to either Th1 or Th2 seems important. By definition, Th1 cells are a subset of CD4⁺ T helper cells that activate macrophages and elaborate Th1-cytokines such as IFN- γ and IL-2 and facilitate the production of specific cytotoxic T lymphocytes. Th2 cells are a subset of CD4⁺ T helper cells that induce B-cells produce antibody (humoral immunity) and suppress the action of cytotoxic T-cells. Th2 cells secrete IL-4, IL-5, IL-10 and IL-13 [184,188]. Macrophages induced by Th2 cells are called M2 macrophages

and they promote tumor growth and progression by elaborating the immunosuppressive cytokine, IL-10. Pro-inflammatory chemokines produced by the infiltrating leukocytes or the neoplastic tissues recruit *Th2* cells and regulatory T cells (T_{reg}) [1]. T_{reg} cells are specialized subset of $CD4^+$, $CD25^+$ T cells that suppress the immune attack against self-antigens and avoid autoimmunity. Tumor derived TGF- β can convert $CD4^+$, $CD25^-$ T cells to $CD4^+$, $CD25^+$ T cells that allow immune evasion by the tumor cells [189]. In Hodgkin's lymphoma, there is overproduction of Th2 cytokines and chemokines attracting Th2 cells [190]. One specific example is an inflammatory chemokine, CCL2, which induces Th2 polarization as evidenced by the inability of CCL2 deficient mice to mount a Th2 response [191]. These data suggest that a high level of CCL2 in the tumor environment may drive the immune response towards a Th2-mediated phenotype, which mediates humoral immunity and suppresses anti-tumor activities.

In addition to tumor influences on Th1/ Th2 polarization, T_{reg} recruitment is responsible for the immune suppression during tumor development. CCR4 expressing T_{reg} are attracted to the tumor site by CCL22, a ligand for CCR4, secreted by tumor cells and macrophages within the tumor environment. CCL2 and CCL5 are also known to cause T_{reg} influx to the peripheral inflamed tissues [188]. These T_{reg} cells suppress tumor specific T cell immunity. High infiltration of T_{reg} is thus associated with poor survival in ovarian carcinoma patients [192]. Wei *et al.* showed that plasmacytoid DCs induced $CD8^+$ regulatory T cells and these T cells express CCR7, respond to CCL19, and exhibit immunosuppression in ovarian cancer patients [193].

4) Other cells of the immune system

Chemokine mediated recruitment of neutrophils to the neoplastic sites has been suggested as a tumor defense mechanism. Hirose *et al.* and Lee *et al.* observed that ovarian cancer cells transfected with a CXCL8 expression vector did not have a defective growth rate *in vitro*, yet they were severely impaired in their ability to form tumors in nude mice. These growth impaired tumors were associated with abundant neutrophil infiltrates [194,195]. When transfected into the cancer cells, CCL7 also possesses similar abilities to recruit neutrophils (in addition to DCs) to the tumor and reduce tumorigenicity [196].

Natural killer (NK) cells have been implicated in inhibition of the progression to metastasis. Human lung adenocarcinoma cells transfected with CCL2, a chemokine involved in augmenting the cytotoxic activity of NK cells, did not undergo metastatic spread compared to the parental or mock transfected cancer cells. This event was NK cell-dependent [197].

IV) Endothelial cells

Chemokine and Chemokine Receptor Expression on Endothelial Cells

Angiogenesis—Both chemokines and chemokine receptors have been found to regulate the process of tumor angiogenesis. Early during embryogenesis, blood islands composed of progenitor cells of the hemopoietic system and endothelial cells (angioblasts) differentiate from the mesoderm layer. The formation of blood vessels from differentiating angioblasts and their organization into a primordial vascular network, consisting of the major blood vessels of the embryo, is called vasculogenesis. While vasculogenesis is limited to early embryogenesis, angiogenesis occurs both during development and in postnatal life. Strictly defined, angiogenesis refers to the process of the formation of new blood vessels from pre-existing, parent vessels, and occurs during both normal, healthy processes, as well as disease progression. For example, new blood vessel growth is a requirement in mammalian tissue and organ development, as well as the process of wound healing. However, aberrant angiogenesis is present in tumor development and progression, and is considered a necessary event for the

transition of a benign cluster of cells into a large tumor with the ability to spread and metastasize [198-200]. Blood vessels located within the tumor function both to deliver nutrients to and take waste products away from the rapidly-dividing cancer cells, thereby allowing growth beyond microscopic, dormant cell clusters into large, malignant cancers [200]. In fact, blood vessel density has indeed been correlated to increased tumor malignancy [201-203]. Furthermore, inter-tumoral blood vessel networks can serve as entry points for cancer cells to migrate out of the tumor, enter the bloodstream, and travel to distant sites where they can begin the growth of a secondary, metastatic tumor. Blood vessel density within tumors has also been correlated to higher incidences of metastatic spread [201-203].

Molecular mechanisms of angiogenesis (endothelial cell migration)—The establishment of new blood vessels from parent vessels requires several steps: first, the basement membrane surrounding the parent blood vessel must be degraded, followed by breakage of cell-cell contacts between endothelial cells and subsequent migration of these cells towards the angiogenic stimulus, and finally proliferation of these cells to form the tubular networks of new vessel lumen [204,205]. Due to their ability to induce both migration and proliferation, chemokines and chemokine receptors are ideal candidates for regulators of angiogenic spread. In fact, several chemokines and their cognate receptors have been found directly to regulate angiogenesis, both *in vitro* and *in vivo* [206-211]. Specific chemokine receptors have been reported to be endogenously expressed on endothelial cells, at both the mRNA and functional protein levels [212]. Additionally, chemokine receptor expression on endothelial cells has been reported to be up regulated by other soluble angiogenic and inflammatory ligands during the processes of both wound healing and tumorigenesis [212, 213]. Furthermore, chemokine stimulation of endothelial cells has been shown *in vitro* to induce actin cytoskeletal rearrangement, migration, invasion, and proliferation [214]. Concurrently, many tumors have been reported to express elevated levels of angiogenic chemokines [209,213]. Therefore, chemokine production by tumors can act as an angiogenic stimulus to induce basement membrane degradation through metalloproteinases, as well as migration and proliferation of endothelial cells to result in the generation of new blood vessels within the tumor.

CXC Chemokines

Of the four families of chemokines, CXC chemokines have been shown to play a most extensive role in angiogenesis. Interestingly, this family contains members that can function either to inhibit or to promote angiogenesis. Early evidence suggested that CXC chemokines with ELR motif acted to stimulate endothelial cell migration, proliferation, and *in vivo* angiogenesis. Conversely, chemokines lacking this motif (ELR-) inhibited migration, proliferation, and *in vivo* angiogenesis [215-217]. However, ELR- chemokine CXCL12 and its receptor CXCR4 have been shown to both increase angiogenesis and play an important role in metastatic progression [24]. Interestingly, the mechanism by which CXCL12/CXCR4 stimulates angiogenesis may be different than the mechanism by which the ELR+ chemokines stimulate a similar process. Recently, down regulation of the secreted glycolytic enzyme phosphoglycerate kinase (PGK) through CXCL12/CXCR4 signaling enabled tumor cells to reduce the extracellular angiostatin levels that resulted in an indirect stimulatory effect on angiogenesis. [61].

ELR+ CXC chemokines—The angiogenic, ELR+ chemokines include CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8 [215]. These chemokines can act directly on endothelial cells via their cognate receptors to promote migration, invasion, and proliferation, thereby mediating angiogenesis. *In vitro*, endothelial cells respond to CXCL8 with rapid stress fiber assembly, chemotaxis, proliferation, and ERK 1/2 phosphorylation [214]. Additionally, CXCL1 released from prostate carcinoma cells induces endothelial cell migration and tube

formation *in vitro* [11]. Alternatively, ELR+ CXC chemokines can function in an autocrine or paracrine, serial or parallel, manner. For example, VEGF activation of endothelial cells can lead to up-regulation of anti-apoptotic protein Bcl-2, which can in turn increase the expression and secretion of CXCL8 [218]. Furthermore, NF- κ B activation by numerous growth factors and cytokines can lead to the up regulation of several ELR+ CXC chemokines, including CXCL8 [219]. Recently, CXCL8 has been implicated in a paracrine feed-forward mechanism in which fMLP-activated neutrophils release VEGF and CXCL8, which in turn stimulates surrounding endothelial cells to release CXCL8, resulting in *in vitro* capillary sprouting [220]. Clearly, these results demonstrate the intricate nature in which angiogenic chemokines are regulated within the process of tumor progression.

Putative angiogenic receptor CXCR2—Subsequent to the discovery of the angiogenic chemokines, the search for the angiogenic chemokine receptor(s) was initiated. Chemokine receptors CXCR1 and CXCR2 were the initial candidates, but only CXCL6 and CXCL8 bind CXCR1, whereas all angiogenic chemokines bind to CXCR2 [221]. Both CXCR1 and CXCR2 were found to be expressed on the surface of endothelial cells, but anti-CXCR2 antibodies were found to block CXCL8-induced endothelial cell migration [221]. In addition, neutralizing antibodies to CXCR2 diminished CXCL8-induced stress fiber assembly [214]. Furthermore, the signaling pathways regulated by CXCR2 are essential for cell proliferation, migration, and survival, which are necessary events in angiogenesis [222].

CXCR2 has also been found to regulate angiogenesis *in vivo*. Using the corneal micro pocket assay, ELR+ CXC chemokine-mediated angiogenesis is inhibited in both CXCR2 (–/–) mice and in CXCR2 (+/+) mice in the presence of CXCR2 neutralizing antibody [221]. CXCR2 neutralizing antibody was also found to reduce neovascularization induced by pancreatic cell supernatant found to contain high levels of CXC chemokine [223]. Using a murine model of lung cancer, tumors in CXCR2(–/–) mice demonstrated inhibited tumor-associated angiogenesis and reduced metastatic potential in an angiogenesis-dependent manner, as compared to tumors in CXCR2(+/+) mice [224]. Taken together, these studies establish that CXCR2 is the receptor responsible for the angiogenic activity of the ELR+ CXC chemokines.

ELR- CXC chemokines—The angiostatic ELR- CXC chemokines include CXCL4, CXCL4L1, CXCL9, CXCL10, CXCL11, and CXCL14 [209]. CXCL4 was the first chemokine to be described as having angiostatic activity [225]. However, the recently-isolated CXCL4 variant CXCL4L1 was found to have a more potent angiostatic activity, although only differing from CXCL4 by only 3 amino acids [226]. Although somewhat unclear, several different receptor-independent mechanisms have been proposed to explain the angiostatic activity of CXCL4. It has been proposed that, because of its high affinity for heparin sulfates, CXCL4 binds to and neutralizes surface heparin sulfate side chains of glycosaminoglycans and interferes with the proteoglycan-bystander effect on growth factor activity [227]. Alternatively, CXCL4 has been shown to directly interact with fibroblast growth factor (FGF) and VEGF and inhibit their ability to bind to cell surface receptors [228]. Additionally, there is evidence that CXCL4 prevents dimerization and subsequent activation of FGF [227,228].

The interferon-inducible ELR- CXC chemokines CXCL9, CXCL10, and CXCL11, also have been found to exhibit angiostatic activity. Notably, they have been found to inhibit angiogenesis in response to the ELR+ CXC chemokines, FGF, or VEGF [211]. In addition, CXCL9 overexpression was found to result in the inhibition of NSCLC tumor growth and metastasis *via* a decrease in tumor-associated angiogenesis [229]. CXCL10 was found to inhibit both CXCL8 and bFGF-induced angiogenesis both *in vitro* and *in vivo* [230].

Putative angiostatic receptor CXCR3—Currently, CXCR3 is the chemokine receptor considered to regulate the angiostatic effects of the ELR- CXC chemokines. CXCR3 is

expressed on human microvascular dermal endothelial cells (HMECs), and CXCL9, CXCL10, and CXCL11 inhibit the IL-8 induced migration of these cells [231]. Furthermore, increased CXCR3 expression was found on human microvascular endothelial cells (HMECs) during S/G2-M phase, and both CXCL10 and CXCL11 block proliferation of these cells *in vitro* [232]. A role for CXCR3B mediated angiostasis *in vivo* has also been reported. In a murine model of melanoma, tumor cells secreting wild-type CXCL10 showed remarkable reduction in tumor growth compared to control, vector-transfected tumor cells [101]. Furthermore, Burdick *et al*, have shown that CXCL11 inhibits angiogenesis in a CXCR3-dependent manner in a murine model of pulmonary fibrosis [233]. Taken together, these data indicate that CXCR3 engagement by ELR- CXC chemokines is essential for the angiostatic activity of select CXCR3 ligands.

CXCR4—CXCL12 has been widely implicated in the promotion of angiogenesis. The CXCL12 receptor, CXCR4, has been found to be expressed on human intestinal microvascular endothelial cells, and CXCL12 can stimulate chemotaxis and proliferation of these cells in addition to promoting endothelial tube formation [234]. CXCL12 was also found to increase the expression of VEGF by endothelial cells, and, in a positive feedback loop, VEGF was found to up regulate CXCR4 on endothelial cells [235]. Additionally, the inhibition of the CXCL12/CXCR4 axis was found to decrease the growth of gastrointestinal tumors through the suppression of angiogenesis [236]. However, the source of CXCL12 within tumors remains unclear. It has been proposed that tumor-associated CXCL12 is secreted from specialized stromal cells within tumors, or carcinoma-associated stromal fibroblasts (CAF) [23]. Conversely, Schrader *et al*, demonstrated the absence of CXCL12 within both renal cell carcinoma cell lines as well as patient specimens [237]. In support of these findings, CXCL12/CXCR4 was found to mediate metastasis, but not angiogenesis, in both breast cancer and NSCLC [43,62]. More recently, however, CXCL12/CXCR4 has been implicated in the recruitment and retention of recruited bone marrow-derived circulating cells (RBCCs) to sites of active neovascularization [210]. Furthermore, preventing the retention of these cells using CXCR4 inhibitor blocked angiogenesis *in vivo* [238]. The role of bone marrow-derived endothelial progenitor cells (EPCs) in neovascularization remains controversial as a number of studies failed to detect these cells in tumors [239 Gothert, 2004, 15187022, Schatteman, 2007, 16980351]. Many studies, on the contrary, do point to a role that bone marrow derived EPCs can play in the neovascularization of the tumor [240 Davidoff, 2001, 11555605, Peters, 2005, 15723071, Duda, 2006, 16339405]. Also, increased circulation of bone marrow derived EPCs in the blood indicates a poor survival rate. Although much evidence exists to implicate the CXCR4/CXCL12 axis in angiogenesis and neovascularization, more direct studies are needed to definitively establish a role for this chemokine in angiogenesis-mediated tumor progression.

CC Chemokines—The CC family of chemokines has also been implicated in angiogenic progression and development. CCL2 can also act as a potent pro-angiogenic factor [241]. In the rabbit corneal angiogenesis assay, CCL2 was found to exhibit similar angiogenic potency to the specific angiogenic factor VEGF-A [242]. Furthermore, CCL2 was found to induce the migration of human endothelial cells at nanomolar concentrations, and this effect was consistent with the expression of CCR2, the receptor for CCL2, on endothelial cells [69]. CCL2 stimulated angiogenesis was through the up regulation of VEGF-A gene expression and the increase of MT1-MMP surface expression and activity in human endothelial cells [243,244]. Furthermore, CCL2 was found to mediate TGF- β stimulated angiogenesis by recruiting vascular smooth muscle cells (VSMC) toward endothelial cells *in vitro* and inducing the formation of new blood vessels [245]. Unlike VEGF-A-induced angiogenesis, however, angiogenesis induced by CCL2 was associated with a prominent recruitment of macrophages [242]. Some evidence suggests that CCL2 expression in tumor tissue may mediate angiogenesis

indirectly via the recruitment of macrophages, and the subsequent production of angiogenic growth factors such as TNF- α and cytokines IL-6 and IL-8 [67,246]. Whether direct or indirect, CCL2 is an important mediator of tumor angiogenesis and may represent a promising therapeutic target for cancer therapy.

In addition to CCL2, other members of the CC family of chemokines have been shown to modulate angiogenesis. CCL1, CCL11, CCL15, CCL16, and CCL23 have all been shown to induce endothelial cell migration *in vitro* and mediate angiogenesis *in vivo* [247-251]. Furthermore, CCL5 and CCL23 have been shown to upregulate MMP9 and MMP2, respectively, implicating their activity in angiogenesis and tumor progression [252,253]. Interestingly, CC chemokine CCL21 (SLC/6C-kine) has been shown to promote anti-angiogenic activity by binding to and activating CXCR3, providing more evidence that CXCR3 is the putative receptor for angiostatic chemokine activity [187,254].

CX₃CL1/ Fractalkine—CX₃CL1 is a novel chemokine in that it can exist either as a secreted molecule, or a molecule that is tethered to the extracellular surface of cells [255]. This chemokine can be produced by, and subsequently tethered to, endothelial cells, attracting CX₃CL1 receptor CX₃CR1-expressing cells. Cells expressing CX₃CR1 include monocytes and specific subsets of T-cells, defining a role for CX₃CL1 in inflammatory processes, disease, and angiogenesis [256]. One report exists indicating the expression of CX₃CR1 on human endothelial cells, and stimulation with CX₃CL1 results in migration and proliferation of these cells [257].

Non-signaling “decoy” receptors (DARC/Duffy)—The non-signaling or “decoy” receptor DARC (Duffy antigen receptor for chemokines) is a seven-transmembrane receptor that binds to both select CC and CXC chemokines, but lacks the DRYLAIV motif in the second intracellular loop. Therefore, DARC can bind chemokines, but cannot couple with G-proteins and initiate subsequent signaling cascades [258]. This apparent lack of G-protein signaling has led to the idea that these receptors act as “sinks” for chemokine, simply binding up circulating chemokine and resulting in internalization and subsequent sequestration [259]. Because DARC has been shown to bind the angiogenic ELR+ chemokines CXCL1, CXCL5, and CXCL8, it was thought that overexpression of DARC by tumor cells would bind and sequester them, reducing tumor angiogenesis by inhibiting endothelial cell migration and proliferation [260]. Addison *et al.* have recently reported that DARC overexpression in non small cell lung carcinoma cells (NSCLC) results in increased tumor necrosis [261]. Furthermore, expression of DARC by NSCLC cells was also associated with a decrease in blood vessel density and a decrease in metastatic potential [261]. In breast cancer, DARC overexpression was found to act as a negative regulator of both tumor growth and metastatic potential through a negative regulation of tumor angiogenesis [262]. Subsequent to DARC overexpression in metastatic breast cancer cell lines MDA-MB-231 and MDA-MB-435, a decrease in angiogenic chemokines was found *in vivo* [262]. With respect to prostate cancer, tumors from DARC-deficient mice had higher intra-tumor concentrations of angiogenic chemokines, increased tumor vessel density, and greatly augmented prostate tumor growth [263]. Finally, transgenic mice expressing the mouse homolog to DARC (mDARC) on endothelial cells under the control of the preproendothelin promoter/enhancer (PPEP), exhibited a diminished angiogenic response to the mouse homolog of CXCL8 (MIP-2) [260]. Taken together, these data indicate that DARC does indeed act as a sink for free chemokine, and that expression within either tumors or on endothelial cells will significantly reduce angiogenic potential.

V) Stromal fibroblasts

Historically, the role of the microenvironment in tumorigenesis is elegantly demonstrated by the *in vivo* experiment in which there was suppression of the oncogenic potential of Rous

sarcoma virus (RSV) when injected into chick embryonic extracellular matrix (ECM) and its environment [264]. But the tumorigenic potential of RSV is realized by simple wounding of the embryo that activated the fibroblasts indicating a critical role for stromal cells in tumorigenesis [265-268].

Stromal fibroblasts from the tumor microenvironment play a critical role in epithelial tumorigenesis [269]. There is significant diversity of gene-expression among primary fibroblasts isolated from different organs, highlighting the critical role played by the microenvironment under physiological circumstances. This might be due to site-specific differentiation of the fibroblasts following migration into specific locations in the developing embryo. Tissue-resident normal fibroblasts are involved in wound healing, production of extracellular matrix (ECM) (type I, III, V collagen and fibronectin), regulation of inflammation and epithelial differentiation. During such remodeling of the tissue or wound repair, fibroblasts are activated to secrete cytokines, growth factors and matrix metalloproteinases that degrade ECM.

Similarly in the tumor microenvironment normal or resting fibroblasts get activated, but they secrete and deposit more ECM (desmoplasia) and matrix metalloproteinases [270]. Such activated subsets of fibroblasts are called cancer or tumor-associated fibroblasts (CAFs / TAFs), reactive stromal fibroblasts or myofibroblasts [267,271]. TAFs form the bulk of the tumor stroma as identified by their expression of α -smooth muscle actin (α -SMA) which is absent in tissue-resident normal fibroblasts. One has to exercise caution when identifying TAFs since other cells, like vascular smooth muscle cells, pericytes and myoepithelial cells, also express α -SMA. Therefore it is important to include other fibroblast markers for validation of TAFs [272].

The mechanism of conversion of normal fibroblasts to TAFs is not well understood currently. Normal, quiescent fibroblasts obtained from breast can be induced to acquire the phenotype of TAFs by TGF- β 1 *in vitro* [25,273]. TGF- β signaling in fibroblasts can also modify nearby epithelial cells [274]. TGF- β may facilitate tumor growth by augmenting angiogenesis and suppressing immune surveillance even though TGF- β has tumor suppressor function in early stages of tumorigenesis [275]. Cancer cells secrete TGF- β , platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF2) and these can activate the normal fibroblast in a paracrine fashion with the emergence of TAFs. Fibroblasts that overexpress TGF- β and hepatocyte growth factor (HGF) promote tumorigenesis of normal breast epithelium while normal resident fibroblasts inhibit tumorigenesis [276].

Experimental studies involving co-culture of tumor cells and fibroblasts and tumor reconstitution in mice from cells obtained breast tumor point to a critical role for tumor-resident fibroblasts in the rate and extent of tumor progression [23,277]. This happens through elaboration of CXCL12 by the stromal fibroblasts. Experimental mouse models and human xenograft studies indicate that mutations or genetic modifications in the stromal fibroblasts can also initiate epithelial tumors [274].

Chemokines and tumor-associated fibroblasts (TAFS)

TAFs are the main source of CXCL12 in any tumor microenvironment. Orimo *et al* [23] reported that when *ras*-transformed MCF-7 breast carcinoma cells (independent of estrogen) mixed and injected with carcinoma-associated fibroblasts subcutaneously in nude mice, grew into large tumors than when injected with normal fibroblasts. The enhanced tumor size was due to increased tumor cell proliferation and not of proliferation by CAFs. These CAFs elaborated CXCL12 that recruited bone-marrow derived endothelial cells that directly increased the proliferation rate of MCF-*ras* tumor cells. In another study, when TAF conditioned media was added to human, initiated but non-malignant hyperplastic prostatic

epithelial cells (BPH-1 cells), or cocultured with TAFs promoted tumorigenesis of BPH-1 cells associated with induction and cell surface expression of the chemokine receptor CXCR4 [151]. Also, the tumorigenic effect can be reproduced by short term incubation of BPH-1 cells with TGF- β . This exemplifies the co-operation between the TAFs that elaborate CXCL12 (ligand for CXCR4) and the initiated prostatic epithelial cells through secretion of TGF- β contributing to prostatic tumor progression [151].

The tumor suppressor p53 attenuates tumor cell migration and metastasis by down-regulating CXCL12 mRNA in stromal fibroblasts [278]. This may explain why genetic mutations that disable p53 transcription factor are frequently observed in many tumor types.

VI) Chemokine and chemokine receptor based therapy

Once the mechanistic details of the primary tumor progression become clear, one can design small molecule drugs to intervene at very early stages before the tumor is firmly established. This requires early detection coupled with therapeutic intervention. But recently, attempts have been made to molecularly phenotype the tumor upon biopsy, determine what pathways and molecular targets are amplified, and then use a tailor-made therapeutic regimen or marker-guided therapy to target the tumorigenic pathways altered for that particular patient.

Some relevant molecular targets for developing anti-cancer drugs are CXCR4-CXCL12 axis (to block metastasis), the transcription factor STAT3 (to rejuvenate the immune system and increase immune surveillance and tumor clearance that had been subverted), lysyl oxidase (LOX) (blockade of LOX has been shown to abolish metastasis), cyclooxygenase-2 (COX-2) (to block the production of the inflammatory prostaglandin PGE2 often associated with colorectal cancer and several other cancer types), hypoxia inducible factor (HIF-1- α blockade of HIF-1- α will decrease CXCR4 surface expression and lysyl oxidase in the ECM) inducible nitric oxide synthase (iNOS) (blockade of iNOS will prevent immune suppression by tumor cells), nuclear factor-kappa B (NF- κ B) (blockade of NF- κ B will abolish transcriptional up regulation of many chemokines, cytokines involved in tumor progression and metastasis and will block expression of anti-apoptotic factors) and Akt (blockade of Akt along with Bcl2-XL for non-small cell lung carcinoma will annihilate any survival potential of the tumor cells). Usually, targeting a single molecular target may not be successful and a combination of two or more molecular targets may prove beneficial.

Based on the involvement of CCR7 / CCL21 in lymph node metastases and CXCR4 / CXCL12 involvement in lung, liver, bone marrow and brain metastases, the disruption of the CXCR4 / CXCL12 axis using small molecule pharmacological inhibitors may prove successful, coupled with the early detection of the primary tumor.

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Fig1.

Tumor and stromal cells influence each other mutually through chemokines and cytokines resulting in tumor growth and the presence of specific chemokines in distant organs and chemokine receptors on the tumor cells set up distinct patterns of metastasis for a given type of cancer.

- 1) The list of chemokines and cytokines elaborated by different stromal cells are enlisted - Dendritic cells (DCs) – CCL16, CCL17, CCL18, CCL22, CX3CL1 (immature DCs) and CCL22; Carcinoma-associated fibroblasts – CXCL12; Endothelial cells – CXCL12, CCL5, CX3CL1; Th1 cells – IL-1, IL-2, TNF- α , IFN- γ , LT- β ; TH2 cells – IL-1, IL-4, IL-5, IL-6, IL-10, IL-13; Tumor associated macrophages (TAMs) – CCL2, CCL18, CCL20, CXCL9, CXCL10 and CXCL11.
- 2) The chemokines in different organs are enlisted - Salivary gland, Colon, Trachea, Mammary gland – CCL28; Epidermal keratinocytes of the skin CCL20, CCL27; Intestines – CCL20, CCL25, CX3CL1; Bone marrow – CXCL12; Lymph node- CCL21, CXCL8 and CXCL12; Lungs – CXCL12, CXCL8
- 3) The chemokine receptors on different stromal cells are enlisted - Immature dendritic cells – CCR1, CCR3, CCR5 and CXCR1; Mature dendritic cells – CCR7, CXCR4; Naïve T-cells – CXCR4 and CCR7; Activated T-cells – CXCR5, CXCR3; TH2 cells – CCR4, CCR8; Natural killer (NK) cells – CXCR3, CCR5; Treg Cells– CCR4; Endothelial cells – CXCR1, CXCR2,

CX3CR1; Microvascular dermal endothelial cells – CXCR3; Intestinal microvascular endothelial cells – CXCR4

Table I

Chemokine superfamily and their receptors

Systematic name	CXC Chemokine Human	Mouse	Chemokine Receptor	P/M
ELR+ chemokines				
CXCL1	MGSA- α /GRO- α	GRO/MIP-2	CXCR2>CXCR1	P
CXCL2	MGSA- β /GRO- β	GRO/MIP-2	CXCR2	P
CXCL3	MGSA- γ /GRO- γ	GRO/MIP-2	CXCR2	P
CXCL4	PF4	PF4	Unknown	A
CXCL5	ENA-78	GCP2 / LIX?	CXCR2	P
CXCL6	GCP-2	GCP2 / LIX?	CXCR1, CXCR2	P
CXCL7	NAP-2	Unknown	CXCR2	P
CXCL8	IL-8	Unknown	CXCR1, CXCR2	P
ELR- chemokines				
CXCL9	Mig	Mig	CXCR3	A
CXCL10	IP-10	IP10CRG2	CXCR3	A
CXCL11	I-TAC	I-TAC	CXCR3	A
CXCL12	SDF-1 α / β	SDF1/PBSF	CXCR4, CXCR7	M, P
CXCL13	BCA1	BLC	CXCR5	
CXCL14	BRAK / Bolekine	BRAK	Unknown	P
CXCL16	SR-PSOX	Unknown	CXCR6	
CCL1	I-309	TCA3 / P500	CCR3	P
CCL2	MCP-1 / MCAF	JE?	CCR2	P
CCL3	MIP1 α / LD78 α	MIP1 α	CCR1, 5	P
CCL3L1	LD78 β	Unknown	CCR1, 5	
CCL4	MIP1 β	MIP1 β	CCR5	P
CCL5	RANTES	RANTES	CCR1, 3, 5	P
(CCL6)	Unknown	C10 / MRP1	Unknown	
CCL7	MCP-3	MARC?	CCR1, 2, 3	P
CCL8	MCP-2	MCP-12?	CCR3, 5	P
(CCL9/10)	Unknown	MRP2 / CCF18 / MIP1 γ	CCR1	
CCL11	Eotaxin	Eotaxin	CCR3	P
(CCL12)	Unknown	MCP5	CCR3	
CCL13	MCP-4	Unknown	CCR2, 3	
CCL14	HCC-1	Unknown	CCR1, 5	
CCL15	HCC-2 / LKN-1 / MIP1 δ / MIP5	Unknown	CCR1, 3	P
CCL16	HCC4 / LEC / LCC1	Unknown	CCR1, 2	P
CCL17	TARC	TARC / ABCO2	CCR4	
CCL18	DC-CK1 / PARC / AMAC1	Unknown	Unknown	P
CCL19	MIP3 β / ELC / Exodus-3	MIP3 β / ELC / Exodus-3	CCR7	P
CCL20	MIP3 α / LARC / Exodus-1	MIP3 α / LARC / Exodus-1	CCR6	P
CCL21	6Ckine / SLC / Exodus-2	6Ckine / SLC / Exodus-2 / TCA4	CCR7	P, Lymph node metastasis
CCL22	MDC / STCP1	ABCD1	CCR4	
CCL23	MPIF1 / CK β 8 / CK β 8-1	Unknown	CCR1	P / M
CCL24	Eotaxin-2 / MPIF2	MPIF2	CCR3	
CCL25	TECK	TECK	CCR9	
CCL26	Eotaxin-3	Unknown	CCR3	
CCL27	CTACK / ILC	ALP / CTACK / ILC / ESkin	CCR10	
CCL28	MEC	Unknown	CCR3, 10	
XCL1	Lymphotactin / SCM1 α / ATAC	Lymphotactin	XCR1	
CX ₃ CL1	C chemokine CX₃CL1 chemokine Fractalkine	Neurotactin / ABCD3	CX ₃ CR1	P/M

P — Tumor Progression; M — Metastasis; A - Angiostatic